American Journal of Medical Genetics 64:78–79 (1996)

Letter to the Editor

Gene Localisation for Sutherland-Haan Syndrome (SHS:MIM 309470)

To the Editor:

The syndrome of X-linked mental retardation (borderline/mild/moderate in affected men), short stature, microcephaly, brachycephaly, small testes and spastic diplegia was characterised and tentatively mapped to the pericentromeric region from a single family [Sutherland et al., 1988]. The lod score of 1.61 at recombination fraction 0.13 for the marker *DXYS1* (Xq21.3) was increased to 2.10 by inclusion of a boy tentatively assessed as affected (IV-16 in the report of Sutherland et al. [1988]). The few informative RFLP markers available at that time all showed recombination; thus, a regional localisation could not be determined. No other families with this disorder have been reported.

This family is now revisited. Patient IV-16 has not changed significantly since the original report was written. As he has grown older we have been able to confirm that he is intellectually disabled and that his spastic diplegia is a persisting problem. The initial assessment of intellectual functioning at 1 year 11 months showed a developmental quotient in the low average range but the circumstances of the assessment were less than ideal and the psychologist considered the result tentative and recommended repeat testing. This was performed at 4 years 2 months and showed

TABLE I. Two-Point Lod Scores Between SHS and 20 Marker Loci

	θ								
Loci	0.001	0.01	0.05	0.1	0.2	0.3	0.4	Z max	$\hat{\theta}$
DXS538	−10.66	−5.70	−2.39	−1.12	−0.12	0.21	0.22	0.24	0.35
CYBB	−10.67	−5.71	−2.40	−1.14	−0.14	0.18	0.19	0.22	0.36
DXS7	−2.57	−0.61	0.61	0.96	1.0	0.70	0.26	1.04	0.15
MAOA3	−1.97	−0.01	1.19	1.52	1.50	1.15	0.61	1.57	0.15
MAOA	−2.27	−0.32	0.87	1.18	1.16	0.81	0.31	1.24	0.14
DXS1003	4.33	4.27	3.99	3.63	2.84	1.96	0.99	4.34	0.0
SYN1	4.33	4.27	4.00	3.65	2.87	1.99	1.01	4.34	0.0
PFC	4.33	4.27	3.99	3.63	2.84	1.96	0.99	4.34	0.0
DXS426	4.33	4.27	4.00	3.65	2.87	1.99	1.01	4.34	0.0
DXS573	4.33	4.27	3.98	3.60	2.77	1.83	0.80	4.34	0.0
DXS991	3.73	3.68	3.46	3.17	2.50	1.74	0.88	3.74	0.0
ALAS2	4.33	4.27	4.00	3.65	2.87	1.99	1.01	4.34	0.0
AR	4.33	4.27	4.00	3.65	2.87	1.99	1.01	4.34	0.0
PGK1P1	4.33	4.27	3.99	3.63	2.84	1.96	0.99	4.34	0.0
DXS1125	1.03	1.98	2.45	2.44	2.06	1.48	0.76	2.47	0.07
DXS106	1.33	2.28	2.72	2.68	2.24	1.59	0.82	2.73	0.07
DXS453	−4.97	−2.02	−0.14	0.47	0.73	0.56	0.19	0.73	0.19
DXS559	1.03	1.99	2.46	2.47	2.10	1.51	0.78	2.50	0.07
DXS566	0.43	1.39	1.91	1.97	1.75	1.32	0.74	1.98	0.09
DXYS1X	0.43	1.39	1.89	1.91	1.60	1.07	0.42	1.93	0.08

Received for publication August 8, 1995; revision received December 18, 1995.

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borderline abilities-mild mental retardation. We considered the boy affected when first seen by us but decided that it was appropriate to be conservative for the purpose of a linkage study.

A detailed genetic background map of the region containing many new highly polymorphic markers is now available. Marker genotypes and lod scores were determined as described by Gedeon et al. [1994]. Linkage is now firmly established with maximum two-point lod scores of 4.34 for several marker loci (Table I). Recombination events detected at *MAOA* (Xp11.3) and at *DXS1125* (Xq12) define the closest loci flanking SHS which now maps within an interval of 22 cM.

The XXX female (III-5), who caused a problem for the 1988 linkage analysis, was removed from the analysis by placing her two sons up one generation as sons of their grandmother whose chromosomes they inherit. The grandpaternal haplotype was not transmitted to either boy. This reduced the information by one meiosis but allowed the recombinants detected in these boys to be used for determining the regional localisation.

The regional localisation for *SHS* refined to the region Xp11.3-Xq12 facilitates delineation of this disorder from other syndromes with similar phenotype. One form of spastic paraplegia (SPG2) is caused by mutations within the proteolipid protein (PLP) locus (Xq21-q22). Pelizaeus-Merzbacher disease is a clinically distinct but allelic variant of the same locus [Saugier-Veber et al., 1994]. The localisation now reported for *SHS* does not overlap with *PLP,* which excludes the possibility that *SHS* might be a further clinical variant at the *PLP* locus. Sutherland et al. [1988] excluded allelism between Juberg-Marsidi syndrome (MIM309590) and SHS on clinical grounds; however, clinical distinction alone is no longer sufficient to exclude allelism given a growing list of clinically distinct but allelic series of conditions [Romeo and McKusick, 1994]. Juberg-Marsidi syndrome was subsequently mapped to Xq12-q21 between *DXS159* and *DXYS1* [Saugier-Veber et al., 1993]. The overlap with *SHS* is less than 3 cM (assuming a distance of 3 cM between *DXS159* and *DXS453*), which suggests that Sutherland et al. [1988] were probably correct in asserting that SHS was distinct from Juberg-Marisidi syndrome.

ACKNOWLEDGMENTS

We thank Sue White for collection of blood samples. This work was supported by the National Health and Medical Research Council of Australia.

NOTE ADDED IN PROOF

The *XNP* gene responsible for ATR-X syndrome is within 350 kb of *PGK1* [Gesz et al., 1994; Hum Mol Genet 3:39-44], and distal to the localisation for Sutherland-Hann syndrome. The *XNP* gene has been implicated in one family with Juberg-Marsidi syndrome [Villard et al., 1996; Nature Genet 12:359-360]. This excludes allelism between Sutherland-Hann syndrome and Juberg-Marsidi syndrome.

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